claims are fully supported by the specification and thus Applicants submit that no new matter has been added by way of any of the above amendments.

II. THE REJECTIONS

A. The Examiner's Rejection Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

The Examiner has rejected claims 27, 29, and 37-39 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. While Applicants do not mean to acquiesce in the Examiner's rejection, Applicants have amended the claims in a sincere attempt to expedite the prosecution of this case.

As will be appreciated, Applicants' amendments have rendered moot the Examiner's concern that claim 39 lacked antecedent basis in claim 37. Moreover, in accordance with the Examiner's suggestion, Applicants have amended the composition claims to recite a "pharmaceutically acceptably carrier." Applicants thank the Examiner for this helpful suggestion.

With respect to the Examiner's concern regarding Applicants' use of the term "extraneous protein" in the claims, Applicants' amendments have deleted this term thus rendering the Examiner's

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rejection moot.[1/] Furthermore, Applicants have amended claim 29 (new claim 40) to delete the term "polyvalent."

For these reasons, Applicants submit that no basis exists for maintaining a rejection of the claims under 35 U.S.C. § 112, second paragraph. Withdrawal of this rejection is respectfully requested.

B. The Examiner's Rejection Under 35 U.S.C. § 102(b) Should be Withdrawn

The Examiner has rejected claim 29 under 35 U.S.C. § 102(b) as allegedly being anticipated by Coulter et al. as evidenced by Stedman's Medical Dictionary (1977). Applicants traverse this rejection.

As is well established, in order to properly maintain a rejection under 35 U.S.C. § 102, each element of the claimed invention must be found in a single prior art reference. However, the teachings of Coulter et al. (as evidenced by Stedman's Medical Dictionary) do not satisfy this requirement.

Applicants' claimed invention concerns antivenin compositions and F(ab) fragments which bind specifically to a venom of a species of the Crotalus genus. Coulter et al., on the other hand, concerns an F(ab) fragment raised against a single neurotoxin isolated from the venom of the Australian brown snake, Pseudonaja textilis.

1/ Applicants note that in their previous response dated October 5, 1995, claims 27 and 29 were amended to delete the phrase "essentially free from extraneous protein." Thus, Applicants assume that the Examiner's continued rejections of claims 27 and 29 in the Office Action dated November 27, 1995 was made in error.

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Clearly, Coulter et al. only concerns an F(ab) fragment to a single toxin of whole venom from a completely different genus of snake. Thus, having failed to teach each element of the claimed invention, Coulter et al. cannot properly be cited for rejecting Applicants' claims under 35 U.S.C. § 102(b). Applicants therefore request that this rejection be withdrawn.

C. The Examiner's Rejection Under 35 U.S.C. § 103 Should be Withdrawn

The Examiner has rejected claims 27, 29 and 37-39 under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary (1977). Applicants traverse this rejection.

To properly maintain a rejection under 35 U.S.C. § 103, the Examiner has the initial burden of establishing a *prima facie* case of obviousness. Meeting this burden requires the Examiner to show first that the prior art would have suggested to those of ordinary skill in the art that they should make the claim composition or device, or carry out the claim process. Second, the Examiner must establish that the prior art would have revealed that in so making or carrying out, those of ordinary skill in the art would have had a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). In the present case, neither requirement has been satisfied.

In maintaining the obviousness rejection of the claimed invention, the Examiner combines the teaching of numerous

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references, attempting to reconstruct Applicants' claimed invention. The Examiner cites Sullivan et al. for teaching a method of purifying whole polyvalent antivenin antibodies against venom of the Crotalus genus. Recognizing that Sullivan et al. do not teach antivenin F(ab) fragments, the Examiner cites Coulter et al. for teaching a method of producing F(ab) antibody fragments.

In an attempt to justify combining the teachings of Sullivan et al. and Coulter et al., the Examiner points first to the teachings of Smith et al. Specifically, the Examiner focuses on the discussion in Smith et al. for allegedly teaching "the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications." See Office Action dated November 27, 1995 at page 5.

The Examiner apparently believes that the use of digoxin specific F(ab) fragments for reversal of digoxin intoxication would have (1) suggested to a person of ordinary skill in the art to prepare F(ab) fragments to <u>any</u> toxin, including snake venoms, and (2) supplied the expectation that such F(ab) fragments could be used successfully for treating the toxic effects of any such toxin. The Examiner also relies on Coulter et al., apparently attempting to supplement the suggestion and expectation of success allegedly supplied by Smith et al. Applicants respectfully submit that neither Smith et al. nor Coulter et al. provide these necessary elements.

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1. Smith et al. Fails to Provide the Requisite Suggestion and Expectation of Success Needed To Maintain An Obviousness Rejection

Applicants seriously question the Examiner's conclusion that the teachings of Smith et al. would have suggested to a person of ordinary skill in the art at the time of Applicants' invention to make F(ab) fragments and compositions which specifically bind a venom of a species of the Crotalus genus. First of all, Smith's use of F(ab) fragments concerns digoxin intoxication and not treatment of snake venom poisoning. Digoxin and snake venom are completely different molecules, and given their dissimilarities, the teachings of Smith et al. certainly would not have suggested making Applicants' claimed F(ab) fragments and compositions for treating the toxic effects of snake bites.

Indeed, digoxin is a small molecule that is ingested and dispersed in the bloodstream and interstitial fluid. Snake venoms, on the other hand, are large hydrophobic molecules that are injected into the muscle or fatty tissues and slowly released from the site of the bite. Moreover, the F(ab)-digoxin complex is relatively small because of the molecular weight of digoxin (781 daltons) does not add substantially to the molecular weight of the F(ab) fragment (50,000 daltons). Venoms, on the other hand, comprise several proteins in the molecular weight range of 20,000-90,000 daltons.

Because of such differences between digoxin and snake venom in both size and mode of action, Smith et al. would have provided no suggestion to make Applicants' claimed antivenin F(ab)

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fragments and compositions. Thus, a person skilled in the art at the time of Applicants' invention would not have been motivated to combine the teachings of Sullivan et al. and Coulter et al. as suggested by the Examiner.

Even if the Smith et al. would have provided a suggestion to make F(ab) fragments to snake venom, the unpredictability of using F(ab) fragments for neutralization and clearance of toxic substances makes it clear that no expectation of success would have existed. As recently as 1994, the art confirmed the unpredictability of using F(ab) fragments to treat the toxic effects of toxins. Such art directly contradicts the Examiner's suggestion that Smith et al. would have provided the expectation of success to make F(ab) fragments to <u>any</u> toxin, including snake venom, for therapeutic applications.

To demonstrate that the art would not have provided the requisite expectation of a success for neutralization and clearance of any toxic substance, Applicants discussed in detail at least two articles which indicated that F(ab) fragments were not effective in neutralizing toxic compounds. Indeed, Faulstich et al. attempted to use F(ab) fragments to treat another toxin -- α-amanitin, which causes mushroom poisoning. However, Faulstich found F(ab) fragments ineffective in neutralizing this toxin. In fact, the toxicity of α-amanitin was 50-fold higher in mice given a F(ab) fragment than in controls. See Faulstich et al. at pages 493-494.

Even as recently as 1994, those skilled in the art continued to recognize the unpredictability of antibody therapy of toxicity.

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Balthasar et al., who used digoxin as a model drug for studying antidrug antibody fragments, cited Faulstich's work as evidence of the "formidable hurdles" that must be addressed in immunotherapy: "The risk of redistributing systemic toxicity, rather than minimizing systemic toxicity, should be appreciated as a potential outcome of the proposed approach." See Balthasar et al. at page 378, right column.

Thus, this evidence clearly contradicts the Examiner's assertion that a reasonable expectation of success would have existed. Despite this fact, the Examiner considered Applicants' evidence to be "irrelevant to the discussion at hand." See Office Action dated November 27, 1995 at page 6. Applicants submit, however, that such evidence could not be more relevant.

In any event, if the Examiner continues to believe Applicants' evidence irrelevant to the discussion at hand, then likewise the teachings of Smith et al. would be irrelevant to the obviousness determination of Applicants' claimed invention. However, if the Examiner continues to cite Smith et al. against of Applicants' claimed invention, the Examiner must consider the negative teachings which would support the patentability of the claimed invention. The Examiner cannot pick and choose only evidence which would support an obviousness rejection and at the same time ignore evidence in the record leading to the opposite conclusion.

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2. Coulter et al. Fails to Provide th Requisite Suggestion and Expectation of Success Needed to Maintain an Obviousness Rejection

In attempting to justify combining the teachings of Sullivan et al. and Coulter et al., the Examiner also relies on Coulter et al. to supply the suggestion to make antivenin F(ab) fragments and to provide the expectation that such F(ab) fragments can be used to treat snake toxins *in vivo*. See Office Action dated November 27, 1996 at page 5. Applicants submit that Coulter et al. provides neither.

Applicants' claims are directed to F(ab) fragments and compositions comprising such fragments. These F(ab) fragments bind specifically to a venom of a species of the Crotalus genus. Coulter et al., on the other hand, deals with a completely different genus of snake. More importantly, Coulter et al. merely describes an F(ab) fragment to a single toxin isolated from whole venom from this different snake. See page 199, last paragraph of Coulter et al.

Thus, at best, Coulter et al. took a mixture of antigens and isolated a single antigen from the mixture. Coulter et al. then prepared an F(ab) fragment to the particular isolated antigen. Applicants find it hard to understand how such a teaching would suggest Applicants' claimed invention. First, Applicants started with a completely different mixture of antigens. Second, Applicants did not, as Coulter et al. suggests, isolate a particular antigen from the mixture and prepare an F(ab) fragment to the isolated antigen. Rather, Applicants prepared F(ab) fragments using the entire antigen mixture.

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Even if Coulter et al. could be said to suggest the claimed invention, Coulter et al. would have failed to provide the requisite expectation of success. Indeed, Applicants note that whole venom is made up of numerous toxins. Simply preparing an F(ab) fragment to one toxin of a venom would have provided no indication as to the effectiveness of F(ab) fragments in treating snake bites. Even the *in vivo* testing done by Coulter et al. does not remedy the defects of this reference.

Coulter et al., in testing their F(ab) fragment to the particular neurotoxin of the whole venom first mixed the isolated neurotoxin with the F(ab) fragment prior to administering to the animal. See Coulter et al. at page 201, third paragraph. Thus, Coulter et al. did not attempt to determine the efficiency of F(ab) fragments in treating snake bites, where the whole venom is introduced in the body and the F(ab) fragments are then administered. In fact, if Coulter et al. had attempted to treat an animal having a snake bite with their F(ab) fragments, one would expect the treatment to fail. Indeed, Applicants note that Coulter's F(ab) fragment to a single toxin would not neutralize many other toxins present in whole venom. Accordingly, Coulter et al. do not provide the required expectation of success needed to sustain an obviousness rejection.

3. Declaration Evidence Further Supports the Lack of a Reasonable Expectation of Success

The Declarations by Dr. Sullivan and Dr. Smith confirm the unpredictability in the art at the time of Applicants' invention. Citing to several reasons in support for his conclusion, Dr. Sullivan states that those of skill in the art did not expect

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F(ab) fragments to venom to be useful as antivenin. Dr. Smith also cites to evidence leading to the same conclusion. As discussed above, the cited art does not teach otherwise. In fact, the cited art would not have provided a reasonable expectation of success to use F(ab) fragments to treat snake bites. Applicants respectfully request the Examiner to again consider Dr. Sullivan's Declaration dated September 25, 1995, particularly pages 3 and 9. Applicants also respectfully request the Examiner to reconsider the Declaration by Dr. Smith dated December 20, 1994, particularly pages 2 and 3.

For the above reasons, Applicants submit that a *prima facie* case of obviousness has not been established. Clearly, the cited art fails to provide the required suggestion and expectation of success needed to maintain an obviousness rejection. Accordingly, the Examiner's § 103 rejection should be withdrawn on this basis.

4. Secondary Considerations Further Support the Nonobviousness of the Claimed Invention

Although Applicants need not rely on secondary considerations of nonobviousness to overcome the present rejection, the secondary considerations in this case further support Applicants' position that the claimed invention would not have been obvious. Such secondary considerations can not be ignored by the Examiner. M.P.E.P. § 716.

Applicants have provided substantial evidence of the nonobviousness of the claimed invention. This evidence includes the longfelt need for improved antivenins prior to the present invention. Intact immunoglobulin and $F(ab)_2$ antivenin had been available since at least 1947 and 1969, respectively, and

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virtually no improvements have been made since 1969 despite deficiencies in these products. See Smith Declaration at paragraph 7. Thus, a critical need for improved antivenins existed for many years.

Recognizing the current need for improved antivenin in this country, the FDA has designated the first purified F(ab) antivenin as an orphan drug, and in an effort to assist getting this product on the market as soon as possible, the FDA has provided financial support to the manufacturer to conduct clinical trials. See Exhibit 5 and Exhibit 6 attached to the Response filed January 17, 1995. Clearly, the FDA believes that the present invention is an important improvement over conventional intact antibody and $F(ab)_2$ antivenins. Such satisfaction of a longfelt need is persuasive evidence of nonobviousness. See In re Dow Chemical, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988) ("Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness").

Applicants respectfully request that the Examiner again consider Applicants' secondary evidence of nonobviousness, particularly the longfelt need satisfied by Applicants' invention. Applicants note that the Examiner apparently did not consider Applicants' evidence on this point in maintaining the obviousness rejection. Indeed, the Examiner must provide the reasons why Applicants' evidence is unpersuasive. M.P.E.P. § 716 at 700-85. Applicants note, however, that merely relying on teachings of Coulter et al. or any of the cited references would be insufficient. As discussed, the cited art fails to suggest

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Applicants' claimed invention and certainly does not provide a reasonable expectation of success for using F(ab) fragments to treat snake bites. Thus, neither Coulter et al. nor any of the art relied on by the Examiner would have satisfied the longfelt need in the art. Accordingly, Applicants, by satisfying this longfelt need, should be entitled to a patent for the claimed invention.

SUMMARY

In light of the above remarks, Applicants submit that there is no basis for maintaining the rejection of the claims under 35 U.S.C. §§ 102, 103 and 112, second paragraph. Accordingly, the claims are in condition for allowance and Applicants earnestly solicit early notice of such favorable action.

The Commissioner is hereby authorized to charge any additional fees (or credit any overpayment) associated with this communication to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should be charged to our deposit account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER

By: 
Alan W. Hammond
Reg. No. 35,178

Dated: April 30, 1996

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000